Celiac patients detected during type 1 diabetes surveillance had similar issues to those diagnosed on a clinical basis

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Abbreviations

T1D – type 1 diabetes mellitus; PVA – partial villous atrophy ; SVA – subtotal villous atrophy ; TVA – total villous atrophy ; GFD – gluten-free diet

Abstract

Aim: To establish whether children with type 1 diabetes (T1D) should be routinely screened for celiac disease.

Methods: Clinical and histological data at celiac disease diagnosis and adherence and response to the gluten-free diet on follow-up were compared between 22 children detected by serological screening during T1D surveillance and 498 children diagnosed because of clinical suspicion.

Results: T1D children suffered less from decreased growth (14.3% vs 40.6%, p=0.016) and clinical symptoms (44.5% vs 98.6%, p<0.001) at celiac disease diagnosis than those detected on clinical grounds. There was no difference between the groups at diagnosis in age (median 7.3 vs 7.9 years, p=0.903), gender (girls 55.0% vs 64.0%, p=0.353), presence of anemia (20.0% vs 21.3%, p=0.886), endomysial antibody titers (median 1:500 vs 1:500, p=0.789) and severity of small-bowel mucosal atrophy (p=0.104). Moreover, the groups showed equal adherence (87.5% vs 85.7%, p=0.086) and clinical response (94.7% vs 96.2%, p=0.542) to the gluten-free diet after a median of 13 months´ follow-up.

Conclusion: Celiac patients detected during T1D surveillance had signs of malabsorption and advanced mucosal damage similarly to those diagnosed on clinical basis. Further, the T1D children often suffered from unrecognized gluten-dependent symptoms and showed excellent adherence and response to the gluten-free diet.

Keywords: Celiac disease, Diabetes, Children, Screening

Key Notes:

- Children whose celiac disease was found in regular type 1 diabetes surveillance were comparable to clinically diagnosed celiac patients in terms of serology and histology.
- These screen-detected patients had also often had unrecognized celiac disease symptoms before diagnosis, and showed excellent adherence and response to the gluten-free diet
- The results support active screening for celiac disease in children with type 1 diabetes

Introduction

Over the past few decades we have witnessed a major increase in the clinical prevalence of celiac disease 1. One reason for this rapid change has been the recognition of specific at-risk groups, of which type 1 diabetes (T1D) is one of the best known[2]. Due to the high concurrence of the two diseases many recent guidelines recommend systematic screening for celiac disease in T1D. Nevertheless, screening on a regular basis remains controversial, since these children are often apparently asymptomatic [3-7]. This, together with the fact that these subjects already have another chronic disease requiring continuous care, is considered to predispose to poor adherence to the demanding and socially restrictive gluten-free diet. Accordingly, some previous studies have shown dietary adherence as low as 25-30% in T1D patients with celiac disease [8,9]. It might also be argued that early diagnosis is not necessary, since T1D children may have less severe intestinal damage and thus a lower risk of celiac disease-associated complications [10]. These unsolved issues have led to substantial variation in the implementation of the current diagnostic guidelines and, instead of systematic screening, many clinicians advocate a more personalized and symptom-based approach to celiac disease in T1D [11,12]. However, previous studies have focused mainly on the effects of double-diagnosis in T1D and comparison has not been made between patients with celiac disease only and patients with celiac disease and T1D. [3,5-7,13].

In Finland, the incidence of both celiac disease and T1D is among the highest in the world, and annual screening for celiac disease in T1D children has consequently been carried out routinely since the turn of the century. This provided as with an excellent opportunity to compare clinical and histological characteristics and dietary adherence between celiac children diagnosed due to previous T1D and those found because of clinical suspicion.

Materials and methods

Patients and data collection

The study was conducted at the Center for Child Health Research in the University of Tampere and Tampere University Hospital. The cohort comprised 520 children with a biopsy-proven celiac disease selected from our regularly updated research database. Patient data were assembled from the medical reports and, if inadequate, complemented with personal interviews conducted by a study nurse with expertise in celiac disease. Besides children detected in the clinic or due to screening of groups at risk of the disease, the database also includes children with asymptomatic celiac disease detected in prospective screening studies. These children screened for reasons other than T1D were excluded from the present study, as well as any children with unclear celiac disease diagnosis.

Clinical data, celiac disease serology and other laboratory values, and severity of histological damage were collected on all patients at the time of celiac disease diagnosis. Further, adherence and clinical and serological response to a gluten-free diet were documented. After data collection the study cohort was divided into two groups based on diagnostic approach as follows: 1. Children diagnosed with celiac disease during regular T1D surveillance (T1D group) and 2. Children diagnosed due to clinical suspicion of celiac disease (clinical diagnosis group). Altogether 42 of the study subjects had concomitant celiac disease and T1D. Of these, 22 were diagnosed with celiac disease during annual serological surveillance for T1D and comprised the T1D group (n = 22). The remaining 20 children with diabetes were first diagnosed with celiac disease due to clinical suspicion and developed T1D only later. Because the celiac disease diagnosis was symptom-based and reached prior to the T1D diagnosis, these patients were included in the control group (n=498).

The study protocol and collection of medical reports were approved by the Pediatric Clinic of Tampere University Hospital and the Ethics Committee of the Pirkanmaa Hospital

District. All children and/or their parents gave written informed consent to possible personal interviews.

Data analyses

Clinical evaluation

Severity of symptoms at diagnosis was classified into four groups: 1. no symptoms, 2. mild symptoms (occasionally disturbing gastrointestinal or extra-intestinal symptoms), 3. moderate symptoms (a combination of symptoms or more distracting or frequent symptoms) and 4. severe symptoms (continuous symptoms significantly disturbing daily life). Poor growth was defined as a significant deceleration of growth compared with the nationally standardized reference rate for age and sex, or lower height than that expected based on the mean parental heights [14,15]. Also the possible presence of other chronic conditions such as selective IgA deficiency, autoimmune thyroidal disease and trisomy 21, as well as a family history of celiac disease, were recorded.

Celiac disease serology and laboratory values

Serum endomysial antibodies (EmA) were assessed at the celiac disease research center by an indirect immunofluorescence method using human umbilical cord as a substrate. A dilution of 1: ≥5 for EmA is considered positive, and positive sera is further diluted 1:50, 1:100, 1:200, 1:500, 1:1000, 1:2000 and 1:4000. Transglutaminase 2 antibodies have also been measured routinely in our hospital from the early 2000s, but by reason of the diversity of assays and reference values results are not directly comparable. Serum hemoglobin (g/l) and mean corpuscular volume (fl) values at the time of celiac disease diagnosis were collected from all patients. Anemia at diagnosis was defined as a hemoglobin value below the age- and sex-matched reference in the local hospital laboratory. Due to the known increased risk of autoimmune thyroidal disease in children with celiac

disease and T1D, also serum thyroid stimulating hormone (TSH, mU/l) values were collected when available.

Small-bowel mucosal morphology

Small-bowel mucosal morphology was assessed by hospital pathologists from a minimum of four biopsies taken from the distal duodenum upon gastrointestinal endoscopy. In 2012 and onwards, at least 2-3 biopsies have also been routinely taken from the duodenal bulb. The celiac disease diagnosis is based on the demonstration of villous atrophy with crypt hyperplasia (Marsh III) in well-oriented biopsy specimens. The degree of the mucosal lesion is further categorized as partial (PVA), subtotal (SVA) and total (TVA) villous atrophy. This well-established classification corresponds roughly to Marsh-Oberhuber scores IIIa, IIIb and IIIc.

Dietary adherence and response to treatment

All children with celiac disease were referred to a dietician after the diagnosis for personal dietary guidance. Adherence to the prescribed gluten-free diet was routinely assessed at follow-up visits and grouped into three classes: 1. children who adhered to a strict diet, 2. children with occasional lapses (minor inadvertent gluten exposure less than once a month) and 3. non-compliant children (one or more lapses a month). Good clinical response to the diet was defined as disappearance of clinical symptoms, negative seroconversion or a marked decrease (diet less than 1 year) in celiac autoantibodies and improvement of possible abnormal laboratory values and poor growth.

Statistics

Quantitative data are reported as medians with quartiles. Qualitative and categorical variables are expressed as percentages. The number of patients with available data on each specific variable is

reported in the tables. Normally distributed variables were compared by Student´s t-test and skewed variables by Mann-Whitney U test. Cross-tabulation with χ^2-test was used to detect differences in categorical variables. A P value <0.05 was considered significant in all analyses. Analyses were made on SPSS statistical software package (version 22, IBM Corp., Armonk, NY).

Results

The median age in the whole study cohort (n = 520) was 7.8 years and 63.8% were girls. The median age in the T1D group (n=22) was 7.3 years and 55% were girls, while the corresponding figures in the clinical suspicion group (n=498) were 7.9 years and 64%. In clinically-detected cases, 61.3% had gastrointestinal symptoms and 29.5% extra-intestinal manifestations as the main presentation at diagnosis. Although all patients in the T1D group were diagnosed in diabetes surveillance, 55.0% of them reported unrecognized clinical symptoms or signs at celiac disease diagnosis (Table 1). However, these were less severe than in the clinically diagnosed patients (Fig. 1A). There was no significant difference between the study groups in the severity of small-bowel mucosal atrophy at celiac disease diagnosis (Fig. 1B). Of note, also half of those in the T1D group already had subtotal or total villous atrophy.

The screening-detected T1D children suffered less from poor growth at diagnosis than those in the clinical suspicion group (Table 2). There were also trends towards a lower prevalence of celiac disease in the family and a higher prevalence of thyroidal disease and trisomy 21 in the T1D group (Table 2), whereas diagnosis of celiac disease in toddlers was more common among the clinically detected children (Fig. 1C), the differences being however not significant. No other significant difference between the groups was demonstrated in any of the other clinical, serological and laboratory parameters (Tables 2 and 3).

Patients in both groups showed equal adherence to the gluten-free diet (Fig. 1D). In the T1D group, one child had occasional and one frequent dietary lapses. In the clinical suspicion group 14.0% of the children had occasional lapses, while again only one reported frequent gluten consumption. Response to dietary treatment was also comparable, as 94.7% of the T1D patients and 96.2% of clinically detected children reported symptom relief and showed a significant reduction in celiac autoantibodies while on the diet (p=0.542). In a separate subgroup analysis of the 20 diabetic children included in the clinical suspicion group (celiac disease diagnosed prior to T1D on clinical basis), 70.0% were on a strict diet and 30.0% had occasional lapses. Furthermore, 91.0 % were found to evince good clinical and serological response to the dietary treatment.

Discussion

Our results demonstrate that children diagnosed with celiac disease in the course of T1D surveillance do not differ in most of their clinical, serological and histological parameters from those found on clinical basis. In addition, a substantial proportion of these screening-detected children had unrecognized clinical symptoms, and there was no difference between these two groups in terms of adherence or response to diet. Our findings thus support the view that children with T1D would benefit from regular serological screening for celiac disease.

Despite the different diagnostic approach, almost half of the T1D children reported symptoms at celiac disease diagnosis, and the beneficial dietary response further substantiates the gluten dependency of these symptoms. This is in line with studies carried out in patients detected by other types of at-risk group screenings, for example first-degree relatives of celiac disease patients [10,16,17], and demonstrates that in fact these individuals very often are not asymptomatic but only unrecognized. The prevalence of reported symptoms in patients with concomitant celiac disease and T1D has varied from zero to 85% depending on study design and definition of

symptoms [3,4,6,7,13,18]. It is true that here and also in some previous studies the celiac symptoms in T1D children have been mostly mild [4,19], but it should be realized that even these can cause a substantial burden and reduce the quality of life in the long term. In fact, as patients cannot compare their daily discomfort with that of others, they often accept it as an inevitable part of life and recognize it as a consequence of untreated celiac disease only afterwards on a gluten-free diet [10]. The wide spectrum and unspecific nature of the symptoms constitutes a significant diagnostic challenge to physicians in daily practice, and further supports active screening for celiac disease in T1D patients.

Approximately half of the children in the T1D group here already evinced subtotal or total villous atrophy at celiac disease diagnosis. This is in accord with the few previous studies addressing this topic, which have also found severe atrophy to be common among celiac patients with concomitant diabetes [6,7]. Furthermore, we found no difference between the groups in serum EmA titers at diagnosis. Together these findings demonstrate that, in spite of an often seemingly mild clinical presentation, even screen-detected T1D patients may already have a well-advanced histological and serological disease. It is important to realize that ongoing mucosal damage may predispose unrecognized celiac patients to excessive use of medication and healthcare services [20,21] and to serious long-term complications [22]. Accordingly, several of the T1D children here already had anemia and poor growth at celiac disease diagnosis. Similar results have previously been reported by Tsouka and colleagues [23]. It is thus evident that that these patients are at risk of progressing towards an even more severe disease if not diagnosed and placed on dietary treatment. This issue is of particular importance in T1D children, since it is known that concomitant diabetes further predisposes celiac disease patients to complicated disease [24]. In general, a delay in diagnosis could lead to various consequences of untreated celiac disease [25,26], and screening has recently been

proved to constitute a significant protective factor against delay and the subsequent unnecessary burden of the disease [25].

A necessary prerequisite for active screening for any disease is that the patient adapts to treatment. Thus, one finding of particular importance here was the equal adherence to the gluten-free diet regardless of the diagnostic approach. The high self-reported compliance was further confirmed by the excellent clinical and serological response to the diet. By reason of different study designs it is difficult to compare our study with previous works. For instance, adherence has been estimated using a diversity of serological or histological criteria, patients might have switched from a regular to a gluten-free diet in the course of the study [6, 27], or non-compliant subjects might have been excluded. Notwithstanding these discrepancies, at least one previous study has found compliance in T1D children to be comparable with our figures [28]. Moreover, our results are in line with those of a few recent studies conducted in patients screened for celiac disease for reasons other than preceding T1D [28,29]. One factor promoting good adherence in could be the parents´ desire to optimize their child's health by treating the disease as well as possible, and the frequent follow-up of T1D probably lends further support. In spite of the good results here, we recognize that daily motivation to adherence can be challenging, particularly in asymptomatic individuals with another burdensome disease [30]. In our opinion, however, the families should at least be aware of the presence of untreated celiac disease and the potential associated complications, and consider whether the diet should be started.

Major limitations of the study were the retrospective design and the limited number of children with concomitant T1D and celiac disease. This latter, however, is a consequence of the strict inclusion criteria, as we accepted only children screened in routine surveillance for the T1D group, while the other 20 diabetics in question were placed in the control group, since their diabetes was found subsequent to the celiac diagnosis. Another limitation is that we did not investigate the

effect of the gluten-free diet on the metabolic control of T1D, but based on previous evidence, a well-designed diet may even help to maintain a good glucose balance [7]. It must also be borne in mind that all Finnish children with celiac disease receive monthly financial compensation and the disease is well-known among physicians. Further, observance of a gluten-free diet is relatively easy owing to the good availability of appropriate products in groceries and restaurants. This might not be the case in every country, but we demonstrated that at least in a supportive environment it is possible to achieve excellent dietary adherence in screen-detected celiac patients with concomitant T1D.

To conclude, we showed that the presentation of celiac disease is largely comparable in children found by regular screening during T1D follow-up visits and those diagnosed because of clinical suspicion. In particular, physicians should acknowledge that many T1D children may suffer from unrecognized celiac disease symptoms and have well-advanced villous atrophy with a subsequent increased risk of long-term complications. The excellent adherence and response to the dietary treatment further advocates active screening for celiac disease in children with T1D.

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Figure legend

Figure 1. Severity of symptoms (A), degree of small-bowel mucosal atrophy (B), age distribution (C), and adherence to the gluten-free diet (D) at celiac disease diagnosis in 520 children diagnosed in the course of regular type 1 diabetes surveillance or due to clinical suspicion

Fig. 1A

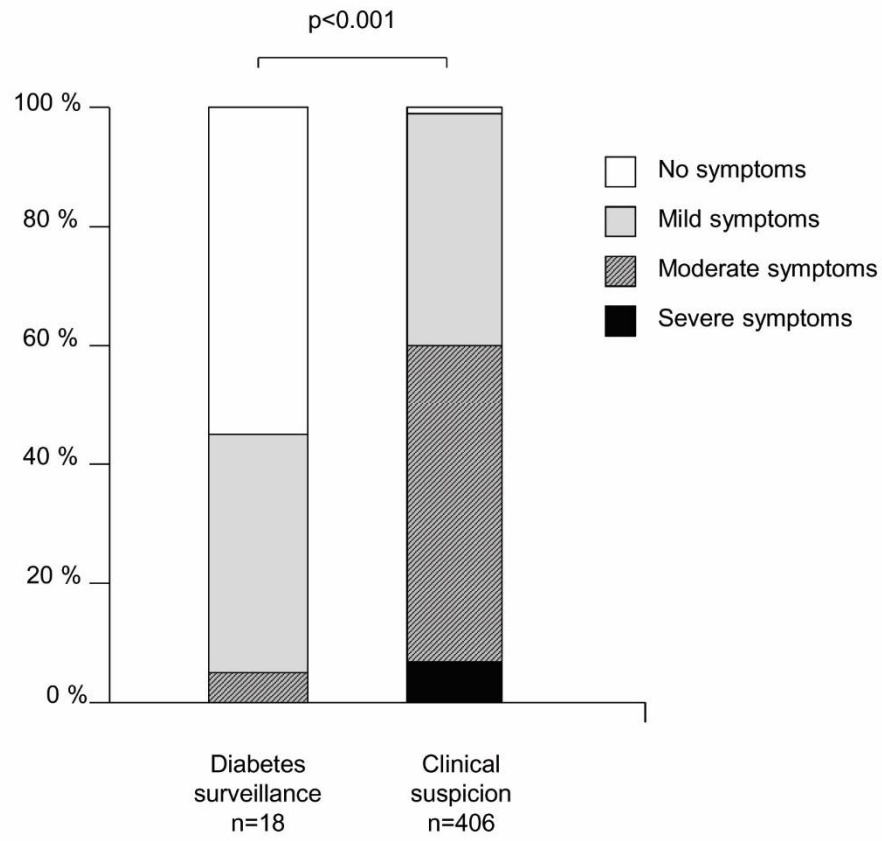
p<0.001
100 %
80 %
60 %
40 %
20 %
0 %
No symptoms
Mild symptoms
Moderate symptoms
Severe symptoms
Diabetes surveillance n=18
Clinical suspicion n=406

Fig. 1B

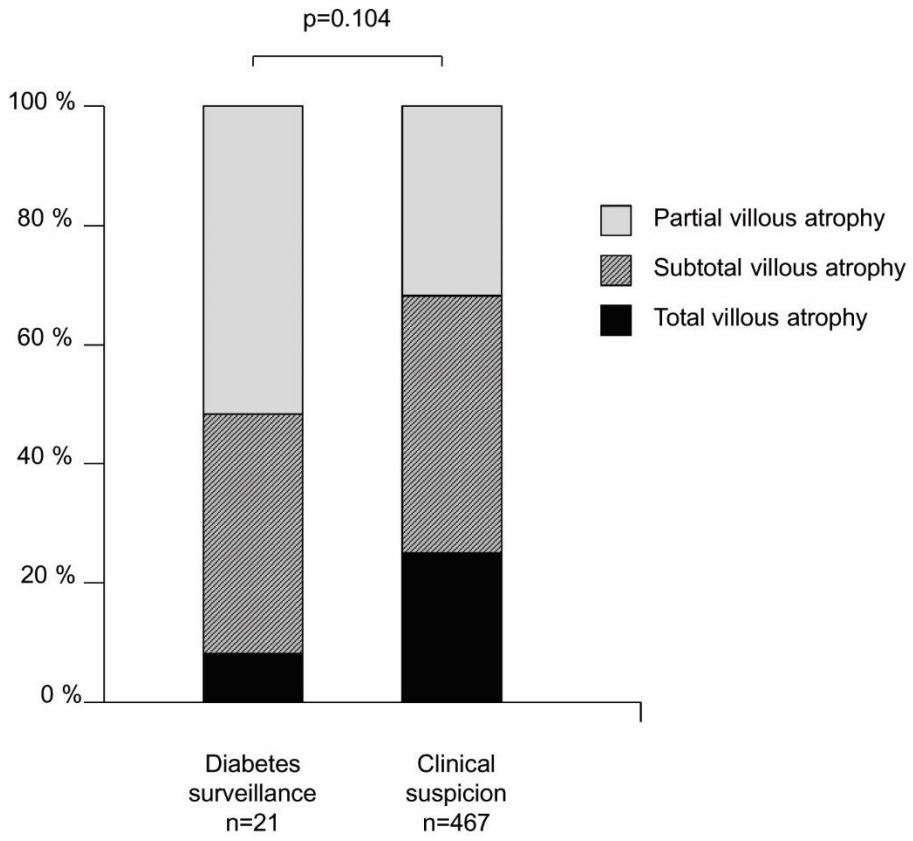
p=0.104
100 %
80 %
60 %
40 %
20 %
0 %
Partial villous atrophy
Subtotal villous atrophy
Total villous atrophy
Diabetes surveillance n=21
Clinical suspicion n=467

Fig. 1C

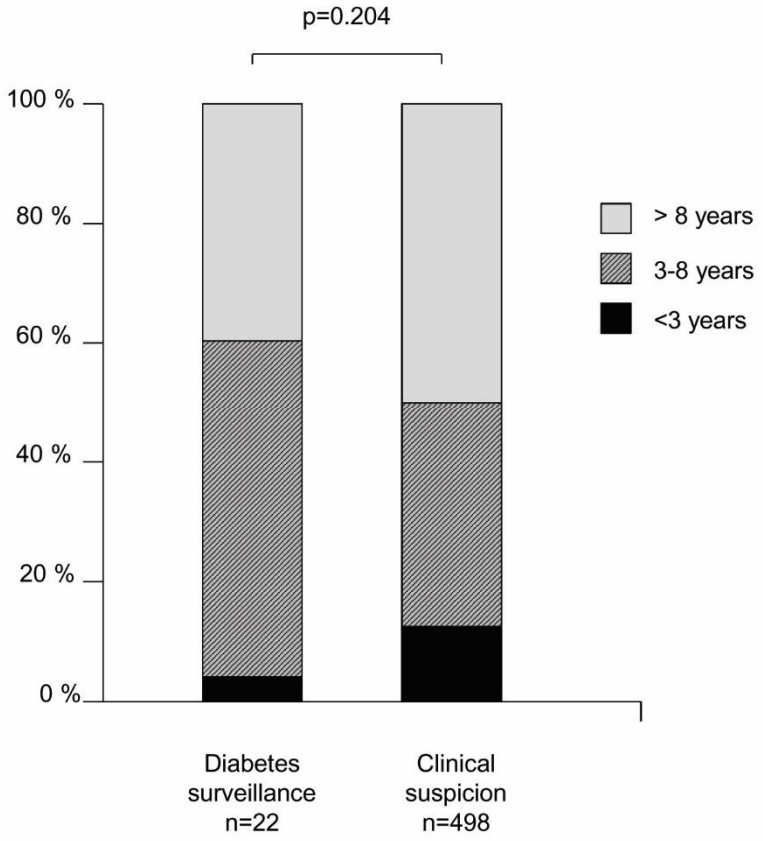
p=0.204
100 %
80 %
60 %
40 %
20 %
0 %
> 8 years
3-8 years
<3 years
Diabetes surveillance n=22
Clinical suspicion n=498

Fig. 1D

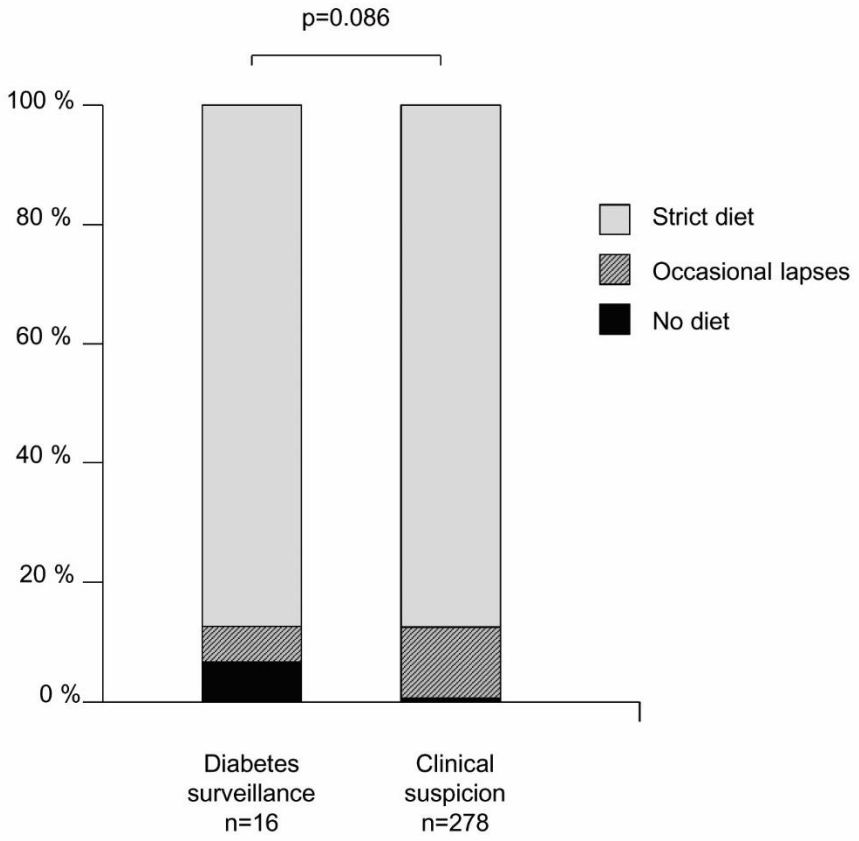
p=0.086
100 %
80 %
60 %
40 %
20 %
0 %
Strict diet
Occasional lapses
No diet
Diabetes surveillance n=16
Clinical suspicion n=278

Table 1. Clinical, histological and serological characteristics at celiac disease (CD) diagnosis in 22 patients screened for CD in the course of regular type 1diabetes (T1D) surveillance.

	Sex	Age at T1D diagnosis, yr	Age at CD diagnosis, yr	Symptoms or signs	Villous atrophy	EmA, titer	GFD
1	M	1.0	2.0	Diarrhea	ND	ND	Strict
2	M	ND[1]	7.0	Stomach pain	PVA	ND	No diet
3	M	3.0	10.0	Poor growth	SVA	1:2000	Strict
4	F	4.5	7.0	None	SVA	1:1000	Strict
5	F	1.0	10.0	None	PVA	1:50	Strict
6	M	ND[1]	11.0	None	TVA	ND	Strict
7	M	ND[1]	7.0	None	TVA	1:4000	ND
8	M	1.9	7.6	None	PVA	1:<5	Strict
9	F	10.2	12.2	None	PVA	1:200	Strict
10	F	8.0	9.6	None	SVA	1:2000	ND
11	F	7.6	7.8	Poor growth, anemia	SVA	1:4000	Strict
12	F	9.3	14.4	Stomach pain	PVA	1:200	ND
13	F	3.8	4.0	Anemia	PVA	1:50	Strict
14	M	14.1	14.2	Poor growth, anemia	SVA	1:1000	Lapses
15	F	15.2	15.3	None	PVA	1:100	ND
16	F	4.2	5.3	Bloating	PVA	1:200	ND
17	F	3.7	4.1	Constipation	SVA	1:1000	Strict
18	F	ND	3.8[2]	Diarrhea	PVA	1:5	Strict
19	M	3.3	5.5	None	SVA	1:100	ND
20	F	5.5	5.5	None	SVA	1:500	Strict
21	M	3.4	6.3	Diarrhea	PVA	1:1000	Strict
22	M	7.6	12.3	Anemia	PVA	1:500	Strict

ND, no data; PVA, partial villous atrophy; SVA, subtotal villous atrophy; TVA, total villous atrophy; EmA, endomysial antibodies; GFD, gluten-free diet,

[1] T1D diagnosis made before CD diagnosis, exact age missing from the database

[2]Time of first positive T1D-specific antibodies, insulin started at the age of 7.8 years

Table 2. Clinical characteristics and prevalence of other concomitant conditions in 520 children screened for celiac disease owing to regular type 1 diabetes (T1D) surveillance or because of clinical suspicion. Values except age at diagnosis are shown as percentages.

	T1D surveillance n=22		**Clinical suspicion n=498**		
	n[1]	**%**	**n[1]**	**%**	**P value**
Age, median (Q_1, Q_3), years	22	7.3 (5.5, 10.8)	498	7.9 (4.3, 11.9)	0.972
Girls	22	55.0	498	64.0	0.353
Celiac disease in the family	13	23.1	253	45.8	0.107
Poor growth at diagnosis	21	14.3	433	40.6	**0.016**
Anemia at diagnosis	20	20.0	431	21.3	0.886
Thyroidal disease	22	9.1	438	2.3	0.108
Trisomy 21	22	4.5	441	1.6	0.325
IgA deficiency	20	0.0	426	1.4	1.000
Other chronic disease[2]	22	31.8	497	28.0	0.726

Q_1 and Q_3, lower and upper quartile

[1]Data available

[3]E.g. epilepsy, asthma, multiple allergies, rheumatoid arthritis, psychiatric disorder, inflammatory bowel disease, congenital heart disease, immune deficiency

Table 3. Laboratory and growth parameters in 520 children screened for celiac disease in the course of regular type 1 diabetes (T1D) surveillance or because of clinical suspicion.

	T1D surveillance n=22		Clinical suspicion n=498		
	n[1]	Median (Q_1, Q_3)	n[1]	Median (Q_1, Q_3)	P value
Hemoglobin, g/l	19	131 (124, 134)	348	124 (114, 131)	0.052
MCV, fl	14	80 (75, 84)	276	81 (76, 83)	0.774
EmA, titer	19	1:500 (1:100, 1:1000)	268	1:500 (1:100, 1:1000)	0.789
TSH, mU/l	11	1.6 (1.1, 3.1)	114	2.5 (1.6, 3.2)	0.123
Height, SD	15	0.3 (-0.2, 1.0)	128	0.1 (-0.7, 0.8)	0.600
Weight, SD	14	-0.5 (-0.6, 0.6)	105	-0.3 (-1.2, 0.4)	0.457
BMI, kg/m^2	16	16.3 (15.0, 17.7)	173	16.2 (14.9, 18.1)	0.426

Q_1 and Q_3, lower and upper quartile; MCV, mean corpuscular volume; EmA, endomysial antibodies; TSH, thyroid-stimulating hormone; SD, standard deviation; BMI, body mass index

[1]Data available